

Evaluation of the Effect of 1,3-Bis(4-Phenyl)-1H-1,2,3-Triazolyl-2-Propranolol on Gene Expression Levels of JAK2–STAT3, NF- κ B, and SOCS3 in Cells Cultured from Biopsies of Mammary Lesions

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Abstract Breast cancer is the most frequent neoplasia in women and is responsible for approximately 13.8% of deaths per year for this gender. It has been suggested that JAK2, STAT3, and NF- κ B gene expression is involved in this type of cancer. The objective of the present study was to determine the effect of bistriazole in these signaling pathways in patients with breast cancer and benign mammary lesions. The inhibitory concentration 50 of bistriazole was calculated in cell cultures of patients with benign lesions, Probit = 4.6 μ M with IC = 95%. The study was performed by examining 63 women who submitted to mammary biopsies. Biopsies of the mammary lesions were performed, gene expression was determined, and cells were cultured in the presence of 4.6 μ M bistriazole. We found that breast cancer is related to age greater than 50 ($P \leq 0.01$), being overweight ($P \leq 0.023$) and having a waist circumference larger than 80 cm ($P \leq 0.01$). The gene expression of JAK2, STAT3, and NF- κ B was higher in groups of patients with breast cancer, while SOCS3 expression was lower. After being exposed to bistriazole, the expression of JAK2 and STAT3 decreased, and the expression of SOCS3 and NF- κ B increased. In conclusion, this molecule in development has an effect on the gene expression of JAK3 and STAT3; nevertheless, the lack of change in NF- κ B indicates that it is not a regulator of inflammation, and therefore, more studies should be performed.

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Introduction

Breast cancer has become an extremely important health issue in Mexico due to its increasing incidence and mortality. In 2009, 4964 deaths were recorded, with a mortality rate of 1.70 per 100,000 women above 25 years old, representing an increase of 30% during the past 20 years (Chávarri-Guerra et al. 2012). The factors that are considered high-risk are age, family history, early menstruation, late menopause, nulliparity, late age of the first pregnancy, obesity, a sedentary lifestyle, the use of hormone replacement therapy, and carrying the BRCA1 and BRCA2 genes (Perks and Holly 2011; Murray and Davies 2013).

In accordance with international guidelines, the established therapy is determined based on the status of HER2 and hormone receptors (PR and ER) and the onset of menopause. The decision for administration of adjuvant chemotherapy is based on age, nodal status, grade, and tumor size. Recently, gene expression profiles have been considered as factors that have high prognostic and predictive values that may be used to provide more personalized and effective therapies. Some examples of gene expression profiles being examined are the signaling pathways of JAK2 (belonging to the Janus kinase that makes up the family of cytoplasmic receptors of tyrosine kinases) (Yun et al. 2012; Gupta et al. 2012; Zou et al. 2011) and STAT3 (signal transducers and activators of transcription), kinases that are involved in the differentiation and development of breast cancer and are often found over-expressed in this disease (Jardé et al. 2011; Haricharan and Li 2014). One of the suppressors and regulators of this pathway is Suppressor of cytokine signaling (SOCS3) (Babon et al. 2012). This suppression can be deregulated or inhibited during carcinogenesis as a result of phosphorylation of STAT3. By inhibiting phosphorylation, the function of the cytokine suppressor is recovered. The activation of JAK2/STAT3 has been widely studied and is now considered a relevant therapeutic target in different types of cancer (Shanmugam et al. 2011).

Among the factors that play a significant role in the development of breast cancer, obesity is of primary interest as it is linked to an increase in angiogenesis and alterations in the serum levels of powerful regulators of cell growth, such as adiponectin, leptin, and estrogen (Jardé et al. 2011). Obesity and being overweight are prevailing conditions world-wide. The World Health Organization (WHO) reports that more than 400 million people are obese and predicts an increase to 700 million by 2015 (Guo et al. 2012; Ray and Cleary 2012).

Processes such as inflammation and the immune response are involved in the development of breast cancer because they represent two of the most significant mechanisms regulating progression of this cancer type that are regulated by nuclear factor-kappa B (NF- κ B). There are several stimuli that can activate the signaling pathway of NF- κ B; among them are the pro-inflammatory cytokines (TNF- α , IL-1, IL-6), bacteria, virus, viral proteins, lipopolysaccharides, and physical and chemical stress. Cellular stress that can activate NF- κ B includes radiation, ionization, chemotherapeutic agents, and reactive oxygen species (ROS) that cause oxidative

stress and, as a result, DNA damage, which causes inflammation and the transcription of genes such as cyclooxygenase-2 (Cox-2), bcl-2, bcl-x1, XIAP, survivin, VEGF, and AKT (Ling and Kumar 2012; Li et al. 2010; Moretti et al. 2012). Among the chemotherapeutic agents that activate NF- κ B are taxol, tamoxifen, paclitaxel, vinblastine, vincristine, doxorubicin, daunomycin, 5-fluorouracil, cisplatin, and bortezomib; therefore, this pathway is highly associated with treatment resistance. The need for new and more effective treatments to reduce the mortality rate caused by breast cancer is urgent.

Several triazoles and bistriazoles possess pharmacological activities, such as antibacterial, anti-fungal, anti-inflammatory, and antitumoral (Duan et al. 2013), with high stability under conditions of acid or basic hydrolysis and oxidation and reduction due to their high aromatic stabilization. Their heterocycles possess large dipole moments that are capable of binding to hydrogen, which favorably forms bonds with biomolecules (Kumar et al. 2012; Hou et al. 2011). It has also been observed that these molecules inhibit the polymerization of tubulin, which is essential for cell division, and the aminopeptidase methionine enzymes (MetAPs) that play an important role in eliminating methionine, an indicator of synthesis of new polypeptide chains. In humans, some proteins with this inhibitory activity have been described: METAP, MetAP1, and MetAP2, which play critical roles in the proliferation and growth of cells of various types of tumors (Kumar et al. 2012).

The aim of this study was to evaluate the activity of the bistriazole 1,3-bis(4 phenyl)-1H-1,2,3-triazolyl-2-propanolol in cell cultures from mammary biopsies through gene expression analysis of JAK2/STAT3, NF- κ B, and SOCS3 in a cell culture of biopsies from mammary lesions.

Materials and Methods

Study Design

This was a prospective cross-sectional study performed on patients from the Maternal–Perinatal Hospital “Mónica Pretelini Sáenz” (HMPMPS), Health Institute of the State of Mexico (ISEM), Toluca, State of Mexico during the period of August 2013 to March 2014.

Patients

We evaluated women whose profiles showed a high probability of potential breast cancer, excluding those with antineoplastic treatment and hormonal therapy.

Anthropometric Characteristics

Weight (kg), height (m), and waist circumference of all of the patients who participated in the study were recorded. Women were classified according to their body mass index (BMI) as normal weight ($\text{BMI} < 24.9 \text{ kg/m}^2$), overweight ($24.9 \text{ kg/m}^2 < \text{BMI} < 29.9 \text{ kg/m}^2$), or obese ($\text{BMI} > 30 \text{ kg/m}^2$).

Laboratory

Approximately, 10 mg of the biopsy was cultivated (culture medium RPMI 1640, Sigma-Aldrich, Germany) and exposed to 1,3-bis(4 phenyl)-1H-1,2,3-triazolyl-2-propanolol for 48 h at a concentration of 4.6 μ M. Subsequently, RNA was extracted with the MagNA Pure Lc RNA Isolation Kit III (Roche, Germany) in the MagnA Pure LC 2.0 (Roche, Germany). The RNA was diluted to a concentration of 10 μ g of cDNA (High Capacity RNA-to-cDNA, Applied Biosystems). In the real-time polymerase chain reaction (RT-qPCR), specific probes for STAT3 (Hs 01047580_m1), JAK2 (Hs 01078124_m1), NF- κ B (Hs 00765730_m1), SOCS3 (Hs 02330328_s1) were used, with 18 s (Hs99999901_s1) as a control gene (TaqMan[®] Gene Expression Assays-Inventoried, Applied Biosystems, UK). These values were quantified in the 7500 Fast Real-Time PCR System (Applied Biosystems, UK). All molecular studies were processed at the Laboratory of Molecular Biology, Medical Sciences Research Center (CICMED), Autonomous University of the State of Mexico (UAEMex), Toluca, Mexico.

Samples

Biopsies directed by ultrasound-guide (Voluson E8, GE Healthcare, USA) or stereotaxy (MultiCare Platinum prone breast biopsy table, Hologic, Germany) selected through the BI-RADS (Breast Imaging Reporting and Data System) scale (grade 4 a, b, c), of suspicious lesions of malignancy. The sampling was directed by ultrasound-guide specific to injury so that the amount of stromal tissues and inflammatory cells did not interfere with the mammary cancer epithelia to measure RNA levels.

Inhibitory Concentration 50 (IC50)

Analysis was performed with the Probit model and, according to calculations for the point of 50% of dead cells, the inhibitory concentration 50 (IC50) was found to be 4.6 μ M, with a confidence interval (CI) of 95%. The results were analyzed with the statistical program IBM SPSS, version 22.

Study Ethics

This study was approved by the Ethics Committee of the HMPMPS (2010-12-156), and it was performed under the strictest ethical standards of the Declaration of Helsinki, Fortaleza, Brazil. Informed consent was obtained from all study participants.

Statistical Analysis

A Student's *t* test and the Mann–Whitney *U* test were performed to determine if there were significant differences among the study groups; a multiple correlation was established to determine the association between expression levels of JAK2/STAT3, SOCS3, NF- κ B, and their suppression with the bistrizole. The F-test was used to evaluate differences of proportions among the study groups; for such purposes, we used SPSS, version 22 software.

Results

Patients

Sixty-three female breast biopsy samples were obtained, and two groups were formed with these samples: the control group with benign lesions ($n = 42$) and the breast cancer group with malignant lesions ($n = 21$). Table 1 shows anthropometric measurements and the grade of gene expression of the biopsies before and after being exposed to bistriazole and its statistical significance. Sampling was directed by ultrasound-guide specific to injury so that the amount of stromal tissue and inflammatory cells did not interfere with the mammary cancer epithelia to measure RNA levels.

Gene Expression

According to the statistical data, we observed that the gene expression of STAT3, JAK2, and NF- κ B was higher in the cancer group than in the control group; in the case of SOCS3, the expression was lower in the cancer group.

The Pearson correlation was used to analyze gene expression of the biopsies before being subjected to bistriazole treatment, and a moderately statistically significant association between the expression of STAT3 and JAK2 ($rP = 0.734$,

Table 1 Anthropometric characteristics and gene expression of the population surveyed

Variable	Control group $n = 42$ Average \pm SD	Group with cancer $n = 21$ Average \pm SD	<i>P</i>
BMI (kg/m ²)	25.52 \pm 3.96	27.58 \pm 2.97	0.017
Age (years)	44.98 \pm 15.3	53.24 \pm 9.53	0.036
Weight (kg)	62.51 \pm 11.5	67.93 \pm 6.45	0.011
Height (m)	1.56 \pm 0.68	1.56 \pm 0.56	0.901
Waist circumference (cm)	89.01 \pm 11.71	94.54 \pm 8.16	0.026
Hips circumference (cm)	98.65 \pm 11.11	105.54 \pm 6.13	0.006
STAT3 ^a	1.12 \pm 1.0	8.39 \pm 3.6	0.001
JAK2 ^a	0.03 \pm 0.02	2.02 \pm 0.90	0.002
NF- κ B ^a	0.94 \pm 0.8	2.88 \pm 1.4	0.001
SOCS3 ^a	14.27 \pm 11.2	5.08 \pm 3.8	0.005
NF- κ B with bistriazole ^a	28.68 \pm 24	25.15 \pm 15.1	0.78
SOCS3 with bistriazole ^a	344.7 \pm 249	495 \pm 151.9	0.24

BMI body mass index, JAK2 Janus kinase 2, STAT3 signal transducer and activator of transcription 3, SOCS3 suppressor of cytokine signaling 3, NF- κ B nuclear factor B

^a $2^{-\Delta\Delta Ct}$ relative expression using 18S housekeeping gene

Statistical test: Mann–Whitney *U* test and Wilcoxon signed-rank test

p Statistically significant (<0.05)

$p < 0.05$), STAT3 and NF- κ B ($rP = 0.547$, $p < 0.05$), and STAT3 and SOCS3 ($rP = -0.336$, $p < 0.05$) was found, with the former being inversely proportional.

After biopsy exposure to bistriazole, it was observed that gene expression of STAT3 and JAK2 was suppressed in both the control group and the cancer group. In the case of SOCS3 and NF- κ B, bistriazole increased gene expression levels.

The age and circumferences of waist and hips increased as the BMI did. An increase in STAT3, JAK2, and NF- κ B also related to increases in the BMI. On the contrary, SOCS3 showed an inverse correlation to BMI. These results are shown in Table 2.

In the survey applied to the study subjects, the following information was asked: family history of breast cancer, whether they breastfed their children, and if they procreated or not. These data were analyzed with the Student's t test, and the results are shown in Table 3.

No differences between the two studied groups were found in relation to family history of cancer, breastfeeding, and procreation.

Discussion

Over-expression of the JAK2/STAT3 signaling pathway has been proposed as a therapeutic target in breast cancer due to its strong involvement in the proliferation and development of this type of neoplasia (Furth 2014; Santillán-Benítez et al. 2012; Harbeck et al. 2010). Even more, SOCS3 is a cytokine that regulates this signaling pathway (Babon et al. 2012; Linossi et al. 2013) and is able to suppress or

Table 2 Characteristics of the patients and their relation with the BMI

	Normal weight $n = 22$ Average \pm SD	Overweight $n = 32$ Average \pm SD	Obesity $n = 9$ Average \pm SD	p^1	p^2
Age (years)	44.18 \pm 17.3	48.59 \pm 13.18	53.33 \pm 3.7	0.32	0.12
Height (m)	1.56 \pm 0.06	1.57 \pm 0.06	1.53 \pm 0.06	0.65	0.35
Waist circumference (cm)	81.27 \pm 5.95	93.72 \pm 8.3	104.1 \pm 8.9	0.001	0.001
Hips circumference (cm)	91.62 \pm 9.27	105.1 \pm 8.3	108.8 \pm 10.9	0.001	0.001
STAT3 ^a	3.07 \pm 3.8	5.17 \pm 4.7	5.65 \pm 4.7	0.34	0.31
JAK2 ^a	0.02 \pm 0.01	0.9 \pm 0.8	1.7 \pm 2.3	0.12	0.16
NF- κ B ^a	1.47 \pm 1.2	2.30 \pm 1.7	1.45 \pm 1.0	0.38	0.71
SOCS3 ^a	11.76 \pm 11.8	10.46 \pm 9.9	7.19 \pm 6.17	0.98	0.56

BMI body mass index, JAK2 Janus kinase 2, STAT3 signal transducer and activator of transcription 3, SOCS3 suppressor of cytokine signaling 3, NF- κ B nuclear factor B

^a $2^{-\Delta\Delta C_T}$ relative expression using 18S housekeeping gene

Statistical test: Mann–Whitney U test and Wilcoxon signed-rank test

p Statistically significant (<0.05)

p^1 Between normal weight and obesity

p^2 Between overweight and obesity

Table 3 Family history, breastfeeding, and gravida in cases of breast cancer

		Diagnosis		Total	<i>P</i>
		Control <i>n</i> = 42	With cancer <i>n</i> = 21		
Family history of cancer	Yes	8	4	15	1.0
	No	34	17	52	
Breastfeeding	Yes	27	17	44	0.12
	No	12	4	16	
	A little	3	0	3	
Gravida	Had children	32	17	49	0.67
	Didít have children	10	4	14	

Statistical test: student’s *t* test

p Statistically significant (<0.05)

control the over-expression of STAT3. Thus, the function of this cytokine might contribute to the inhibition of proliferation and development of breast cancer cells.

Recently, a Cu(I)-catalyzed synthesis pathway for cycloadditions of azide-alkyne called “click” (CuAAC) was discovered; the bistriazoles can be synthesized more quickly and with higher efficiency and better performance (Harbeck et al. 2010). This reaction is the best route to obtain 1,2,3-triazoles, which have been found to possess interesting biological properties that could be important for the design of new drugs (González et al. 2011; Schweinfurth et al. 2011; Sztanke et al. 2008).

The IC50 from the compound that was evaluated in this study was 4.6 μM; this value is below concentrations obtained by other authors who have worked with triazolic compounds (Xia et al. 2012; Li et al. 2013).

In this study, it was found that 1,3-bis(4-phenyl)-1H-1,2,3-triazolyl-2-propanolol is capable of suppressing the JAK2/STAT3 signaling pathway in cells from breast cancer biopsies at a concentration of 4.6 μM. Additionally, the expression of SOCS3 in these cells also increased as a result of treatment from 5.08 to 459 relative units (RU); therefore, we expect that based on the anti-inflammatory properties of this compound, it would suppress or reduce expression of NF-κB, which participates in the neoplastic processes (Oeckinghaus et al. 2011). The results are shown in Table 1.

A statistically significant association between the expression of JAK2 and STAT3 was found because the former is activated by JAK2. A correlation between STAT3 and NF-κB was also found, as both signaling pathways are activated by interleukins, mainly IL-6 (German et al. 2011; Aizpurua et al. 2010), the pro-inflammatory cytokine over-expressed in overweight and obese patients. Nevertheless, when the cells of a mammary lesion are treated with bistriazole and the expression levels of JAK2 and STAT3 have been suppressed, NF-κB must be activated by other pathways in addition to the JAK2/STAT3 pathway.

A relevant factor leading to breast cancer is obesity that affects the regulation of serum levels of adiponectin, leptin, and estrogens (Jardé et al. 2011). It has been shown that leptin activates the JAK2/STAT3 signaling pathway, contributing to the

development of breast cancer (Napoleone et al. 2012). One way to evaluate obesity is through BMI measurements (Khandekar et al. 2011). In fact, those more likely to develop breast cancer are those who are obese and overweight; moreover, increased BMI values are associated with higher expression of JAK2/STAT3 and NF- κ B and lower expression of SOCS3 (Santillán Benítez et al. 2012), as shown in Table 2.

Factors such as family history of breast cancer, nulliparity, and breastfeeding predispose women to develop breast cancer (Youlden et al. 2012); nonetheless, this study did not find any statistically significant correlation between these factors and breast cancer (Table 3).

A subsequent study evaluates the effect of bistriazole on NF- κ B expression to substantiate the conclusions of the current, performed study, as this compound could activate NF- κ B through other pathways or not interfere with them. As a result, it is important to study the proteins that interfere with the activation of NF- κ B because this pathway could be activated through a canonical or a noncanonical pathway, where different IKKs may participate.

Conclusions

The higher prevalence of breast cancer in Mexico demands innovative alternatives that contribute to the prevention and treatment of this disease. The expression of signaling pathways such as JAK2/STAT3 and NF- κ B could be used as early biomarkers of the disease and as new therapeutic targets that function in the development and progression of breast cancer. Alternative treatments focused on these signaling pathways, as proposed in this first phase of this study, could achieve more effective treatments against breast cancer.

Likewise, the risks posed by both being overweight and obese in the development of breast cancer, for example over-expression of the signaling pathways that alter the normal development of cells due to these ailments, will contribute to raising public awareness about the importance of maintaining a healthy lifestyle.

Future studies will further examine the NF- κ B pathway to dismiss or substantiate the effects of bistriazole. We hope to perform studies in animals to evaluate the signaling pathway of JAK2/STAT3, SOCS3, and NF- κ B with this compound.

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